REMARKS

Interview summary

Applicants thank Examiners Angell and Nguyen for the courtesy extended during the telephonic interview conducted March 15, 2004. All references cited in the December 2, 2003 office action were discussed without agreement having been reached.

Claims 70 - 160 are in immediate condition for allowance

Claims 70 - 74 are objected to as being dependent upon a rejected based claim, but would be allowable if rewritten in independent form including all of the limitations of the base and any intervening claims.

Claim 70 is amended herein to incorporate all of the limitations of claim 25, from which it directly depends. A redundant recitation of the size of the sequence-altering oligonucleotide is deleted. No other amendments have been made. Applicants respectfully submit that claim 70 is now in condition for allowance, and that claims 71 and 72, previously presented, which depend directly or indirectly from amended claim 70, are thus also in condition for allowance.

New claims 79 - 103 depend directly or indirectly from claim 70 and are drawn to individual ones of the human gene targets described with particularity in Tables 10 - 32 of the specification. No new matter has been added, and

applicants submit that the new claims are in immediate condition for allowance.

Claim 73 is amended herein to incorporate all of the limitations of claim 25, from which it directly depends. A redundant recitation of the size of the sequence-altering oligonucleotide is deleted. No other amendments have been made. Applicants respectfully submit that claim 73 is now in condition for allowance, as is previously presented claim 74, which depends directly therefrom.

New claims 104 - 127 depend directly from amended claim 73, each new claim drawn to a subrange of claim 73's "SEQ ID NOs: 1 - 4340," each subrange separately and explicitly disclosed in one of Tables 10 - 32 of the specification. Applicants respectfully submit that dependent claims 104 - 127, incorporating all of the limitations of the allowed claim from which they depend, 37 C.F.R. § 1.75(c), are necessarily free of the art; that each subgenus is fully supported by the specification, in satisfaction of 35 U.S.C. § 112, first paragraph; and that new claims 104 - 127 are thus in condition for allowance.

Claims 75 - 78 are allowed.

New claims 128 - 150 depend directly from allowed claim 75, each new claim drawn to a subrange of claim 75's "SEQ ID NOs: 1 - 4340," each subrange separately and explicitly disclosed in one of Tables 10 - 32 of the specification. Applicants respectfully submit that dependent claims 128 - 150, incorporating all of the limitations of the allowed claim from which they depend, 37 C.F.R. § 1.75(c), are necessarily free of the art; that

each subgenus is fully supported by the specification, in accord with 35 U.S.C. § 112, first paragraph; and that new claims 128 - 150 are thus in condition for allowance.

New claim 151 depends directly from allowed claim 75. Claim 75 recites that the sequence-altering "oligonucleotide includes the sequence of any one of SEQ ID NOs: 1 - 4340"; dependent claim 151 recites that the "oligonucleotide has sequence identical to any one of SEQ ID NOs: 1 - 4340." No new matter has been added, the claim is free of the art and fully supported by the specification, and is thus submitted to be in condition for allowance.

Claims 152 - 160 depend directly or indirectly from allowed claim 78. Claim 152, which depends directly from claim 78, recites that the sequence-altering oligonucleotide "has at least three terminal phosphorothioate linkages," one of the classes of terminal modifications explicitly recited in the Markush group of claim 78. Claims 153 - 160 depend from claim 152 and are drawn to individual ones of the human gene targets described with particularity in Tables 10 - 32 of the specification. No new matter has been added. The claims being free of the art and fully supported by the specification, applicants respectfully submit that claims 152 - 160 are in condition for allowance.

In summary, applicants respectfully submit that claims 70 - 160 are in immediate condition for allowance, and respectfully request the same.

Rejections 35 U.S.C. § 103
Have Been Obviated and Should be Withdrawn

Claims 25 - 38, 40 - 58, and 63 - 69 stand rejected under 35 U.S.C. § 103(a) as having been obvious over Yamamoto *et al.* (*Genetics* 131:811 - 819; "Yamamoto") in view of Meyer *et al.* (U.S. Patent No. 6,136,601), the Examiner further noting that "amending claim 25 to indicate that the oligonucleotide 'consists essentially of' the limitations described in claim 25 would obviate the rejection."

Claims 25 - 30, 37, 38, 40, 44 - 47 and 53 - 62 stand rejected under 35 U.S.C. § 103(a) as having been obvious over Yamamoto in view of Wengel *et al.* (WO 99/14226, "Wengel").

Claims 25 - 30, 37, 38, 40, 44 - 47, 53 - 58 and 63 - 69 stand rejected under 35 U.S.C. § 103(a) as having been obvious over Yamamoto in view of Barrachini *et al.* (U.S. Pat. No. 5,801,154, "Barrachini").

Applicants herein cancel claim 25 in favor of new claim 161 and amend all claims that had depended directly or indirectly from claim 25 to depend instead from new claim 161. For the reasons advanced below, applicants respectfully submit that the rejections have been obviated, and that claim 161 and claims that depend directly or indirectly therefrom[1] are in condition for allowance.

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[1] Claims 26 - 28, 33, 35 - 38, 40 - 54, and 56 - 69 depend from claim 161: claims 25, 29 - 32, and 34 are

New claim 161 recites as follows:

161 (new). A method of targeted chromosomal sequence alteration, the method comprising:

introducing a sequence-altering oligonucleotide into a cell *in vitro*, wherein said sequence-altering oligonucleotide:

is a single-stranded nonhairpin oligonucleotide 17 - 121 nucleotides in length;

has an unmodified DNA domain of at least 8 contiguous deoxyribonucleotides;

is fully complementary in sequence to a first strand of the cell's chromosomal DNA at a chromosomal target sequence, except for one or two mismatches positioned (i) within said oligonucleotide's unmodified DNA domain and (ii) at least 8 nucleotides from said oligonucleotide's 5' and 3' termini; and

has chemical modifications consisting essentially of at least one terminal locked nucleic acid (LNA), or at least one terminal 2'-O-Me base analog, or at least three terminal phosphorothioate linkages, or combinations thereof,

whereby said introduced oligonucleotide directs sequence alteration at said chromosomal target sequence by the cellular repair enzyme machinery.

In order solely to expedite prosecution, and pursuant to the Examiner's suggestion, the chemical modifications of claim 161 "consist[] essentially of" the modifications set forth in the ensuing Markush group,

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canceled herein without prejudice; claims 39 and 55 have previously been canceled.

affirmatively excluding the reactive electrophilic group of Meyer.

The internal DNA domain of at least 8 contiguous deoxyribonucleotides is now more distinctly claimed to be chemically *unmodified*, clarifying that the claim does not read on fully modified oligonucleotides as used in the antisense art, as are described in Baracchini.

The whereby clause, introduced at Examiner Nguyen's suggestion, implicates the biological mechanism that inherently underlies the method, serving in conjunction with the revised preamble to more particularly point out applicants' invention.

Support for claim 161 can be found throughout the specification, including the claims as originally filed, and at the locations previously recited in support of former claim 25. Support for two mismatches as between the sequence altering oligonucleotide and the chromosomal target can be found, for example, particularly at p. 12, lines 3 - 15 of applicants' specification.

Applicants respectfully submit that none of the references, alone or in combination, suggested or motivated applicants' invention, as now more distinctly claimed in claim 161. In particular, there is neither suggestion nor motivation in the art to include the locked nucleic acid (LNA) residues of Wengel as terminal modifications of single-stranded, nonhairpin, sequence-altering oligonucleotides in a method of targeted chromosomal sequence alteration, comprising introducing a sequence-altering oligonucleotide into a cell *in vitro*.

Accordingly, applicants respectfully submit that claim 161 and claims that depend therefrom are nonobvious over the cited art and are in condition for allowance, and respectfully request the same.

Applicants invite the Examiner to call the undersigned if he believes there are any matters left outstanding before allowance of the claims herein.

Respectfully submitted,

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